principles of biochemical signaling pathways that regulate immune responses. This study investigates a novel functionality of the tyrosine kinase zeta-associated protein Zap-70 in T cell signaling pathways, using the quantitative phosphoproteomics data obtained from our experimental collaborators. The Zap-70 alterations in cellular signaling pathways (loss of its function or expression) can cause an unusual form of severe combined immune deficiency (SCID) that often leads to fatal outcomes. Therefore, the analysis of signaling events using computational modeling and modern proteomics technique (e.g., stable isotopic labeling of amino acids in cell culture (SILAC)) provides a network map of possible molecular targets guiding disease diagnosis. Additionally, this network map presents information about the placement of newly observed phosphorylation sites in T cell signaling pathways across a time course after receptor stimulation. In this study, we tested several computational models of Zap-70 T cell signaling pathways to experiment with different hypotheses. Specifically, we calculated the phosphorylation levels of tyrosine residues of N- and C- terminals of immunoreceptor tyrosine-based activation motif (ITAM) for different expression levels of Zap-70 in T cells. We performed fully stochastic signaling simulations using stochastic simulation complier (SSC) developed in our lab and modeling of ordinary differential equations. Subsequently, the sensitivity analysis of deterministic simulations was performed for identifications of key proteins and biochemical reactions in signaling networks that regulate stochastic transitions leading to pathological cellular function. The calculated ITAM phosphorylation levels are well correlated with the corresponding experimental ones. Finally, using our computational modeling, we formulated novel testable hypotheses that can guide future experiments.

1900-Pos Board B630
Accelerating Systems Biology Computation: Rapid Estimation of Equilibrium and Kinetic Quantities via Weighted Ensemble Sampling
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We apply the ''weighted ensemble'' (WE) simulation strategy, previously employed in the context of molecular dynamics simulations, to a number of stochastic systems-biology models. WE is relatively easy to implement, does not require extensive hand-tuning of parameters, does not depend on the details of the simulation algorithm, and can facilitate the simulation of extremely rare events. We examine spatially homogeneous (stochastic chemical kinetics) models that range in complexity from a one-dimensional system to a system with 354 species and 3680 reactions, and also examine spatially resolved 3-D systems (simulated in MCell) containing ~10^3 to 10^6 molecules.
For the stochastic chemical kinetics systems, WE is able to produce accurate and efficient approximations of the joint probability distribution for all chemical species for all time t. WE is also able to efficiently extract mean first passage times for the systems, via the construction of a steady-state condition with feedback. WE exhibits speedups over ''brute-force'' in sampling rare events via the Gillespie direct Stochastic Simulation Algorithm ranging from ~10^12 to ~10^18 for characterizing rare states, and from ~10^2 to ~10^4 for finding mean first passage times.
WE is also used to study rare binding events in spatially resolved 3-D systems simulated with MCell. In a toy model, WE exhibits speed-ups on the order of 10^60 for the characterization of rare binding. We also present our ongoing efforts to apply the WE methodology to a spatial model of a frog neuromuscular junction.

1901-Pos Board B631
Negative Feedback and Crosstalk in the TGF-β Signaling Pathway
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The transforming growth factor-β (TGF-β) signaling pathway transduce extracellular signals into transcrip- tional responses controlling key cellular processes, such as differentiation, proliferation, and apoptosis, through a network of receptors. Defects along of the pathway have been associated with a wide range of diseases, including developmental diseases and a variety of cancer types. Here, we examine the role of the negative feedback through protein products of transcriptional regulation by mediator SMAD proteins in the behavior of the network by analyzing a novel, detailed computational model of the pathway. The model includes macromolecular assembly, receptor trafficking and signaling, activation of two SMAD channels, nucleocytoplasmic shuttling of smad-complexes, and feed-back through inhibitory SMADs. This computational model is able to accurately reproduce and explain experimental data in diverse cell types and our analysis uncovered the importance of negative-feedback-mediated crosstalking between channels in the TGF-β pathway. In addition, we identified key crosstalk points among pathways through literature mining approaches, by constructing a detailed ligand-receptor network for all the members of the TGF-β superfamily and mapping the interactions with other pathways.

1902-Pos Board B632
Spatio-Temporal Regulation of Mitotic Spindle Checkpoints
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Stable microtubule spindle attachments at the kinetochores (KT) - the microtubule binding platform on the chromosome - ensure faithful chromosome segregation in mitosis. Unstable KT-spindle attachment locally activates the spindle assembly checkpoint (SAC) - an inhibitory signal that halts mitotic progression of the entire cell. Only after the last KT gets properly attached, can SAC get silenced and chromosome segregation ensue. However, given the everlasting stochastic fluctuations and large chromosome number in the cell, the mechanism ensuring the robustness in the SAC silencing timing remains elusive. From the stably attached KT, key mitotic players, including SAC, stream toward the associated spindle pole. Incorporating such spatial-temporal regulation, we established a theoretical model that unprecedentedly accounted for the fidelity of SAC silencing. It revealed that spindle poles integrate the poleward streaming from the attached KTs. The unattached KTs divert the poleward streaming, competing with the spindle poles. The diversion disappears upon the last KT-spindle attachment, causing a larger jump in the spindle pole accumulation than all the previous KT-spindle attachments combined. This large jump robustly triggers SAC silencing from the spindle poles after and only after the last KT-spindle attachment. This mechanistic insight accounts for many intriguing observations on mitosis, including the biphasic taxol dosage-dependence of anaphase delay, the distinct SAC silencing patterns in merged cells with two spindles, the size scaling between the mitotic spindle and the cell, and the error-proneness of mammalian oocyte meiosis. We thus established a unified conceptual framework across species - the spatial-temporal regulation ensures the fidelity of SAC silencing.

1903-Pos Board B633
The Role of Cooperativity in Cell Signaling
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Sensory cells use surface receptors to detect environmental stimuli and initiate down stream signaling. Cooperative binding of ligands and ions is known to play a crucial role in enhancing the sensitivity of biochemical processes such as oxygen sensing by hemoglobin, but whether cooperativity enhances the fidelity with which a system can accurately detect a signal in a noisy background is poorly understood. Here, we explore the signal to noise ratio for several classes of cooperative signaling. We show that the signal to noise ratio depends on the number, connectivity, and underlying dynamics of the signaling network.

1904-Pos Board B634
Sensitivity Analysis and Model Reduction Applied to Adapting Biological Systems
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A common problem in systems biology is relating the relevant parameters of a mathematical model to its observed qualitative features. In this work, we study a nonlinear dynamic model of a biochemical system with an underlying network topology. The system is parameterized by a high-dimensional vector and it outputs multiple boolean functionalities. The first part of this work develops a regularized sensitivity analysis to determine parameter/functionality relationships and discusses the conditions under which these relationships may be generalized across parameter vectors and network topologies. The second part of this work discusses a method of reducing a given parameter/functionality relationship on a dense network topology to a similar relationship on a sparser network. Throughout this work, we apply our techniques to an established model of biochemical adaptation.

1905-Pos Board B635
Macromolecular Crowding Effects on Gene Regulation
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Studies of macromolecular crowding have shown its important effects on molecular transport and interactions in living cells. Less clear is the effect of crowding when its influence is incorporated into a complex network of interactions. Here we explore the effects of crowding on a model of gene transcription as a network of reactions involving transcription factors, RNA polymerases, and DNA binding sites for these proteins. The novelty of our approach is that we determine the effects of crowding on the rates of these reactions using